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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/788,974	02/26/2004	Kent Jorgensen	2081-0125P	5458

2292 7590 07/22/2009
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EXAMINER	
KISHORE, GOLLAMUDI S	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
07/22/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/788,974	JORGENSEN ET AL.	
	Examiner	Art Unit	
	Gollamudi S. Kishore, Ph.D	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,9,12-72 and 75* is/are pending in the application.

4a) Of the above claim(s) *25-72* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,9,12-24 and 75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The RCE dated 5-20-09 is acknowledged.

Claims included in the prosecution are 1-3, 9-10, 12-24 and 75.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claim 24 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 24 recites two disease conditions, inflammatory conditions and cancer. However, according to the parent claim 15, the method is for selectively drug targeting to ***neoplastic cells***.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1-3, 9-10, 14-24 and 75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kozak (6,166,089) of record in combination with Kodama (4,372,949), Janjic (6,229,002) and Vermehren (BBA, 1998) of record.

Kozak discloses phospholipid prodrugs wherein the carbon 1 of the glycerol has an aliphatic chain and the carbon 2 has an organic radical and carbon 3 has a phosphatidyl group. According to Kozak the organic radical is released by phospholipase A2 present in the pathological tissue. Further according to Kozak, phospholipid conjugates of drugs that will be cleaved by phospholipase A2 have been known to enhance penetration into cells, enable the formulation of drugs in liposomes and as a form of enterocoating that prevents exposure of the gastric mucosa to the drug (note the abstract, col. 4, line 41 through col. 11, line 9, Examples and claims). In Kozak however, a drug is attached to the phosphocholine moiety on C3 of the glycerol since the purpose is the release of the drug by the endogenous phospholipase which selectively cleaves the drug. Kozak however, teaches the principle of attaching the drugs to phospholipids, that is, the design of these prodrugs which are sensitive to different phospholipases and release the drug by specific phospholipases in pathological tissues (col. 8, lines 9-65). The action of endogenous phospholipase 2 on Kozak's compound would result in the formation of lyso-phospholipids. What is lacking in Kozak however is the teaching of the compound without a drug attached in C3 position. What are also lacking in Kozak are the inclusion of a lipopolymer and the administration of the composition in the form of liposomes.

Kodama teaches that lyso phospholipids have carcinostatic and immunostimulating activities and these compounds along with a phospholipid for the treatment of cancer (col. 1, line 12 through col. 2, line 55. The procedure disclosed by Kodama on col. 7, lines 25-55 is a procedure which results in the formation of liposomes.

. Janjic while disclosing lipid constructs containing PDGF teaches the several advantages of administration of the composition in the form of liposomes and the attachment of PEG to the liposomal surface to shield the liposomal complex from blood proteins and thereby enable it to circulate for extended periods in the blood. According to Janjic, the prodrug is on the outside surface of the liposomes (note the abstract, col. 25, line 5 through col. 28, line 67).

Vermehren while disclosing liposomes containing PEG teaches that PEG not only provide steric hindrance which leads to a decrease in the adsorption and interaction of plasma degrading proteins with the liposomal surface, but also enables PLA2 to have increased catalytic activity on the phospholipid containing liposomes. Based on their studies, Vermehren suggest that one can design and optimize the in vivo degradation of drug loaded liposomes at certain sites, e.g., in extra vascular inflammatory tissue due to an enhanced local concentration of the active PLA2 and an accumulation of polymer -grafted liposomes in such tissue (note pages 31-34).

The use of compounds of Kozak without an additional drug attached to the C3 of glycerol would have been obvious to one ordinary skill in the art if the pathological condition exhibits higher endogenous phospholipase A activity such as cancer since the

released lyso-compounds have carcinostatic and immunostimulating activity. The use of polymer (PEG) containing liposomes for the delivery of the prodrug of Kozak would have been obvious to one of ordinary skill in the art because the advantages of the liposomes and the ability of PEG to prolong the circulation time of the liposomes and increasing their susceptibility to PLA2 in the host pathological tissue and thereby increasing the release of the lysolipid from the phospholipid in Kozak.

Applicant's arguments have been fully considered, but are not persuasive. Applicant argues that claims have been amended to exclude protease inhibitors such as 4, 5, 7-trihydroxyisoflavone, a tyrosine kinase and thus even if the skilled artisan were to use polymer containing liposomes for the delivery of the prodrug of Kozak, he would not arrive at the instant invention as the resultant prodrug would be a tyrosine kinase. This argument is not persuasive since one of the embodiments of Kozak is to use the lipids as protease inhibitors. In example 1 Kozak appears to teach phospholipids which are not attached to compounds such as isoflavones. Applicant argues that Kozak teaches that the compound in example 3 is hydrolyzed by PLD in position 3 to release the protein kinase inhibition. This argument is not persuasive since the product of hydrolysis depends upon the enzymes and there is no evidence presented by applicant to show that Kozak's compounds are not hydrolyzed by phospholipase A2 just as in instant case. Applicant's arguments that Kozak clearly teaches on col. 6, lines 5-8 that one of ordinary skill should not formulate the prodrugs into liposomes. The examiner disagrees since applicant misinterpreted Kozak's statement. At this location, Kozak states, "it is not desirable according to the current invention to formulate the prodrugs into liposomes

since this achieves preferential distribution to specific organs (e.g. liver) or specific cell types (e.g. macrophages) rather than to diseased cells within an organ or cell population". It is the examiner's position that one of ordinary skill in the art would be motivated to include a PEG-lipid in the formulations of Kozak if the targeted organ is not liver (reticuloendothelial system organ) but organs which have high phospholipase activity since Vermehren clearly teaches on page 28 that the PEG polymer chains for a steric hindrance that prevents rapid recognition and removal of the liposomes by phagocytic cells of the reticuloendothelial system. With regard to the unexpected results pertaining to the low haemototoxicity compared to lyso-ether lipids of the prior art, the examiner points out that the example on page 54 of the specification indicates the comparison between ET-18-OCH3 and 1-O-DPPC with 5 mol% 1-O-DPPE-PEG2000. There is no control experiment with 1-O-DPPC without DPPE-PEG or ET-18-OCH3 with DPPE-PEG. Furthermore, the results are not commensurate with the scope of the claims with respect to different phospholipids claimed and the amounts of lipopolymer. Furthermore, no experiments were conducted using glycolipids which are also recited in instant claims.

5. Claims 12-13 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kozak (6,166,089) of record in combination with Kodama (4,372,949), Janjic (6,229,002) and Vermehren (BBA, 1998) as set forth above, further in view of Saxon (Journal of Liposome Research, 1999) or Bally (5,736,155).

The teachings of Kozak, Kodama, Janjic and Vermehren have been discussed above. What is lacking in Kozac, Janjic and Verneren is the administration of the composition with an additional liposome encapsulated drug.

Saxon teaches that anticancer drugs can be used in combination in liposomes (summary).

Bally similarly teaches the encapsulation of two anticancer drugs in liposomes (col. 15, Part C).

The use of an additional liposomal anticancer agent would have been obvious to one of ordinary skill in the art, with the expectation of obtaining an additional effect, since the references of Saxon and Bally show that two anticancer drugs can be used in combination.

Applicant's arguments have been fully considered, but are not persuasive. The examiner has already addressed applicant's arguments regarding Kozak. Applicant argues that though both references mention combination therapy, they does (do) not render obvious the liposomal delivery system. This is not persuasive since as recognized by applicants themselves, these references are combined for the use of combination therapy using the liposomal systems.

Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140

F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claim1-3, 9-10, 14-24 and 75 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 7,166,297. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims in the said patent are drawn to a method of treatment of parasitic infections using the same composition. The composition claimed in the patent is generic with respect to the compounds and the delivery system which is 'lipid based drug delivery system and thus, include compounds and liposomes claimed in instant claims. The species in instant claims are anticipated by the claims in said patent.

8. Claims 1-3, 9-10, 14-24 and 75 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 20, 25-31, 36-47 of copending Application No. 10/239,514. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims in the said copending application are drawn to a method of treatment of inflammatory diseases using the same composition. The compositions in instant claims are anticipated by the claims in said copending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant's arguments have been fully considered, but are deemed to be moot in view of the new rejections.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Krass Frederick can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gollamudi S Kishore/
Primary Examiner, Art Unit 1612

GSK